WEST Search History

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DATE: Tuesday, June 29, 2004

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		DB=USPT; PLUR=YES; OP=AND	
☐	L1	antispore.clm. or anti-spore.clm.	0
☐	L2	antispore or anti-spore	9
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=AND	
☐	L3	antispore or anti-spore	18
☐	L4	L3 not l2	9
		DB=USPT; PLUR=YES; OP=AND	
☐	L5	antitoxin.clm. or anti-toxin.clm.	42
☐	L6	antitoxin or anti-toxin not l5	794
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=AND	
☐	L7	antitoxin or anti-toxin not l5 not l6	1205
☐	L8	(L7 or l6 or l5) and plasma$	447
☐	L9	L8 and steril$	343
☐	L10	L9 and (administer$ or deliver$ or infus$ or inject$)	334
☐	L11	L10 and (treat$ or therapeut$ or prophylac$ or prevent$ or acute$)	333
☐	L12	L11 and (bacill$ or anthra$)	101
☐	L13	L11 and anthra$	29
☐	L14	l13 and plasma$	29
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☐	L16	deriving.clm. and process$.clm. and administer$.clm. and plasma.clm.	1
☐	L17	plasma.clm. and administer$.clm. and (vaccinat$ or inject$).clm.	230
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☐	L20	L18 and plasmaph$ and infusi$ not l19 not l16	3
		DB=USPT; PLUR=YES; OP=AND	
☐	L21	plasmaph$ and (method$ or process$).clm. and administer$.clm.	225
☐	L22	L21 and (immuniz$ or immunis$ or vaccin$)	109
☐	L23	L22 and plasma$.clm.	31
☐	L24	L22 and $globulin.clm.	15
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☐	L26	L25 and plasmaph$	33
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☐	L28	L27 and anthra$	0
☐	L29	L27 and staph$	5
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☐	L34	L33 and (im or intramuscul$ or intra-muscu$)	3
☐	L35	L34 and (ig or igg or gamma or gammaglobulin or $globulin)	3
☐	L36	('4482483' |'4719290' |'4699783')!.PN.	3

END OF SEARCH HISTORY

Search Results - Record(s) 1 through 3 of 3 returned.

L36: Entry 1 of 3 File: USPT Jan 12, 1988

US-PAT-NO: 4719290
DOCUMENT-IDENTIFIER: US 4719290 A

TITLE: Composition of intravenous immune globulin

DATE-ISSUED: January 12, 1988

US-CL-CURRENT: 424/177.1; 424/159.1, 424/170.1, 514/2, 514/6, 530/363, 530/389.5, 530/390.5, 530/419, 530/861

INT-CL: [04] C07G 7/00, A61K 35/10, A61K 39/00

L36: Entry 2 of 3 File: USPT Oct 13, 1987

US-PAT-NO: 4699783
DOCUMENT-IDENTIFIER: US 4699783 A

TITLE: Products and methods for treatment of cancer

DATE-ISSUED: October 13, 1987

US-CL-CURRENT: 424/178.1; 530/389.7, 530/413, 530/419, 530/421

INT-CL: [04] A61K 39/395

L36: Entry 3 of 3 File: USPT Nov 13, 1984

US-PAT-NO: 4482483
DOCUMENT-IDENTIFIER: US 4482483 A

TITLE: Composition of intravenous immune globulin

DATE-ISSUED: November 13, 1984

US-CL-CURRENT: 424/170.1; 424/177.1, 530/363, 530/389.5, 530/390.5, 530/861

INT-CL: [03] A23J 0/00, C07G 7/00, C09H 0/00, A61K 39/00

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☐ 26. 6258360. 18 Oct 94; 10 Jul 01. Prodrugs activated by targeted catalytic proteins. von Borstel; Reid, et al. 424/182.1; 424/152.1 424/155.1 424/174.1 435/188.5 514/49 514/50 536/27.4 536/28.55. A61K039/44 C12N009/96.

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First Hit

L14: Entry 2 of 29 File: PGPB Feb 5, 2004

PGPUB-DOCUMENT-NUMBER: 20040023897
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040023897 A1

TITLE: Methods for preventing or treating disease mediated by toxin-secreting bacteria

PUBLICATION-DATE: February 5, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Caplan, Michael J.	Woodbridge	CT	US	

APPL-NO: 10/ 292392 [PALM]
DATE FILED: November 12, 2002

RELATED-US-APPL-DATA:
Application is a non-provisional-of-provisional application 60/337548, filed November 13, 2001,
Application is a non-provisional-of-provisional application 60/338618, filed November 13, 2001,

INT-CL: [07] A61 K 31/7048, A61 K 31/65, A61 K 31/43, A61 K 31/545, A61 K 31/496, A61 K 31/47

US-CL-PUBLISHED: 514/29; 514/192, 514/200, 514/313, 514/153, 514/253.08
US-CL-CURRENT: 514/29; 514/153, 514/192, 514/200, 514/253.08, 514/313

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

Methods and pharmaceutical compositions for preventing and treating disease mediated by toxin-secreting bacteria. Inventive methods and compositions are suited to preventing or treating infections caused by bacterial toxins that enter host cells via receptor-mediated endocytosis (e.g., the anthrax and diphtheria toxins). Methods comprise a step of administering to an individual a pharmaceutical composition that includes an effective amount of an inhibitor of endosomal acidification. The inhibitor may be a primary amine, a carboxylic ionophore, or a selective inhibitor of the vacuolar proton pump (V-ATPase). The inhibitors of endosomal acidification may be employed in combination with other therapeutics such as antibiotics and antitoxins in order to prevent, treat or cure the disease.

The present invention describes techniques and reagents useful in the treatment of microbial infections, and particularly of infections with anthrax.

RELATED APPLICATIONS

[0001] The present application claims priority to provisional applications U.S. Serial No. 60/337,548 and 60/338,618 both filed Nov. 13, 2001 which are incorporated incorporated herein by reference in their entirety.

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☐ 3. 20040013687. 02 Jun 03. 22 Jan 04. Compositions and methods for transepithelial molecular transport. Simpson, Lance, et al. 424/190.1; A61K039/02.

☐ 4. 20040009178. 11 Feb 03. 15 Jan 04. Immunotherapeutics for biodefense. Bowdish, Katherine S., et al. 424/164.1; 530/388.15 530/388.4 A61K039/40 C07K016/12.

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☐ 10. 20030219752. 17 May 02. 27 Nov 03. Novel antigen binding molecules for therapeutic, diagnostic, prophylactic, enzymatic, industrial, and agricultural applications, and methods for generating and screening thereof. Short, Jay M.. 435/6; 435/320.1 435/325 435/326 435/69.1 435/7.1 530/387.1 536/23.1 C12Q001/68 G01N033/53 C07H021/04 C12P021/02 C12N005/06 C07K016/00 C07H021/02 C12P021/06 C12N015/00 C12N015/09 C12N015/63 C12N015/70 C12N015/74 C12N005/00 C12N005/02 C12N005/06 C12N005/16.

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L35: Entry 1 of 3 File: USPT Jan 12, 1988

DOCUMENT-IDENTIFIER: US 4719290 A
TITLE: Composition of intravenous immune globulin

Abstract Text (1):
An intravenous immune globulin preparation having at least 99% pure globulin protein protein and an anticomplement activity of less than 0.10 C'50 units/mg IgG prepared by: precipitating impurities from Cohn Fraction II in an aqueous-alcohol medium at defined temperature and pH, removing the precipitated impurities, stabilizing the diluted solution with albumin, concentrating the solution and removing the alcohol therefrom. Also prepared by this method, an intravenous, hyperimmune globulin preparation having increased antibody titers to sixteen serospecific strains of Pseudomonas aeruginosa.

Brief Summary Text (3):
The present invention relates to high purity intravenously injectable gamma globulin (IgG) preparations and a process for preparing the same. More particularly, particularly, the invention relates to a product and method of making unmodified, unaltered, undenatured or native gamma globulin molecules of high purity for intravenous administration.

Brief Summary Text (4):
The invention also relates to high purity intravenous hyperimmune globulin preparations having increased antibody titers to sixteen serospecific strains of Pseudomonas aeruginosa and the method of making such preparations.

Brief Summary Text (6):
The immune globulin fraction of pooled human plasma contains antibodies to many viruses and bacteria and thus is effective in the management of various diseases including those associated with Staphylococci, Streptococci, Coli, Pseudomonas, Herpes zoster and pyocyaneus septicemias.

Brief Summary Text (9):
Human immune globulins were first isolated on a large scale during the 1940's by F. J. Cohn. It was also observed that the aggregate formed during the fractionation procedure results in anticomplement activity and that clinical application causes adverse reactivity in the patient.

Brief Summary Text (11):
It has been known to prepare immune globulin containing antibodies by fractioning human blood plasma according to the so-called Cohn-method. It has also been known to further purify immune globulin for administration either intramuscularly or intravenously. While producing some of the desired effects, both kinds of administration have some disadvantages, which at times, may be serious or even life-threatening.

Brief Summary Text (12):
Intramuscular injections of immune globulin have proven effective in raising the level of circulating immune globulin and in decreasing the length, frequency and severity of infections in some patients. There are patients, however, who cannot

achieve adequate immune globulin levels and protection from infection with intramuscular administration of immune globulin. Such patients when treated via plasma therapy experience improvement which indicates that intravenous administration may have advantages over the intramuscular route. Other disadvantages of intramuscular administration of immune globulin include the delayed delayed onset of reaction resulting from the slow diffusion of the substance into the circulation, and inconsistent absorption and local degradation in the muscle where the injection is administered.

Brief Summary Text (13):
With intravenously administered immune globulin adequate levels of circulating antibody could be reached immediately and controlled by the rate of infusion. The intravenous route of administration also overcomes the effects of inconsistent absorption and local degradation in the muscle. Also, patients with small muscle mass or bleeding tendency tolerate an intravenous injection better than an intramuscular injection.

Brief Summary Text (14):
While intravenous administration is the preferred route of administration, the product so administered is not without some serious drawbacks. It is known that intravenously administered immune globulin may cause unpleasant side effects such as as flushing, wheezing back and muscle pain, anxiety and hypotension. It has been observed that these side effects may be due to the activation of complement, secondary to the formation of immune complexes, aggregates of immune globulin and denatured globulin formed during the storage thereof.

Brief Summary Text (15):
The prior art has made great efforts to prepare immune globulin which has lesser anticomplement activity, mainly by decomposing or removing the aggregated or denatured globulin. Such efforts included: enzymatical hydrolysis using pepsin, plasmin, papain, or bacterial proteases; chemical tratment by an acid, propiolactone or the like; conversion of the immunoglobulin into a chemical derivative such as by amidation, alkylation or S-sulfonation; and fractional precipitation of the immunoglobulin using polyethylene glycol or the like.

Brief Summary Text (16):
While these methods seemed to decrease the presence of aggregated or denatured globulin in the final products and consequently lowered the anticomplement activity, activity, they were not without other shortcomings, such as low activity of the antibody, shortened half-life time of the immunoglobulin in the blood, and the presence of some denatured impurities which is believed to cause a decrease in efficacy of the immunoglobulin.

Brief Summary Text (17):
To overcome the above-mentioned disadvantages, the prior art has further proposed various preparative methods for intravenous immunoglobulin. Illustrative of these are the methods disclosed in the following patents:

Brief Summary Text (18):
U.S. Pat. No. 4,256,631 discloses a process for the preparation of immunoglobulin for intravenous administration comprising the purification of immunoglobulin by a combination of a fractional precipitation method in which one or more divalent or trivalent metal salts are added to an aqueous solution of the immunoglobulin and the supernatant is processed by affinity chromatography using as an adsorbant a complex of human IgG and a polyhydroxy polymeric compound. The resultant immunoglobulin is said to be extremely pure.

Brief Summary Text (19):
U.S. Pat No. 4,305,870 pertains to a method for making intravenous plasma derivatives which includes the steps of mixing bentonite and an aqueous solution of

plasma derivatives containing exogenous activity, the bentonite and the mixing time being sufficient to adsorb exogenous activity, and isolating the aqueous phase from the bentonite. Optionally, for the removal of residual exogenous activity, the bentonite-treated aqueous phase is further purified by ion-exchange chromatography. The so-obtained product is said to have an acceptable low content of externally deleterious or exogenous activity.

Brief Summary Text (20):
While the above-noted attempts by the prior art greatly enhanced the success of treatment of various infectious diseases by producing satisfactory immunoglobulin for such treatment, none to our knowledge has produced a natural, unmodified, unaltered and undenatured product which desirably should have the following characteristics: it should contain substantially pure Immunoglobulin G (IgG) so that it is substantially free of naturally occurring IgA and IgM antibodies; it should contain all subclasses of IgG, namely IgG.sub.1, IgG.sub.2, IgG.sub.3, and IgG.sub.4 in substantially the ratio as they occur in blood plasma; spontaneous complement activation should be very low or absent; it should be free of polymeric IgG; and it should have a very low level of trace constituents, such as enzymes which tend to degrade and destabilize IgG during storage.

Brief Summary Text (22):
The native IgG molecule is known to have two types of biological activities, namely, namely, the immune-specific activity and the non-immune-specific or "effector" activity. The immune-specific activity is characterized by binding properties for specific antigens whereby the IgG molecule acts as an antibody. The non-immune-specific or "effector" activity includes binding and activation of complement, opsonic activity, and the binding to specific cellular receptors for the Fc portion of the molecule. Any change in the native IgG molecule which alters, reduces or eliminates either of these two types of activities is referred to as denaturation whether said denaturation is the result of intentional or unintentional chemical or enzymatic modification. Commercial preparations of intramuscular IgG, which are processed withouth chemical modifications, contain aggregated forms of IgG that cause high levels of spontaneously fixed and activated complement and are examples of unintentional denaturation. Examples of intentionally denatured IgG molecules include IgG preparations that are modified with the use of chemicals and/or enzymes in an attempt to improve the safety of intravenous administration. Such intentional denaturation diminishes or even completely eliminates the effector functions of IgG and reduces the total beneficial biological potency of the IgG.

Brief Summary Text (23):
In addition to the desired characteristics described above, a Pseudomonas immune globulin preparation must possess preformed, specific anti-Pseudomonas antibodies. Host defense for Pseudomonas depends upon the presence of adequate numbers of functional phagocyte cells plus serum opsonic activity. Optimal phagocytosis of Pseudomonas occurs in the presence of type-specific Pseudomonas antibody. At least seventeen separate strains of Ps. aeruginosa have been identified by the World Health Organization, many of which show unusual resistance to treatment with antimicrobial drugs. Each strain is characterized by localized infections that may overwhelm the host tissue. Endotoxin, toxin A, elastase and protease are released to further weaken the host's defensive mechanism. Clinical cases in which normal immune defenses are compromised, such as burn, cancer and cystic fibrosis cases are particularly susceptible to infection by Ps. aeruginosa. A fast acting intravenous injection of hyperimmune, polyvalent gamma globulin to enhance specific antibody activity can be of life-saving to these patients.

Brief Summary Text (24):
Anti-Pseudomonas immune globulin, immune whole blood and immune plasma are known in the prior art. Notwithstanding their beneficial properties, their drawbacks include having limited antibody titers, protection against only some of the recognized strains of Ps. aeruginosa, and the lack of high purity.

Brief Summary Text (25):
It is, accordingly, an object of the present invention to provide a native gamma globulin preparation suitable for intravenous injection.

Brief Summary Text (26):
It is another object of the present invention to eliminate undesired denatured properties of IgG not by the alteration of effector functions but by the selective elimination of molecular forms of IgG which are denatured and at the same time eliminate impurities in the form of non-IgG proteins.

Brief Summary Text (27):
It is still another object of the present invention to provide a gamma globulin preparation suitable for intravenous administration, in which anticomplement activity is less than about 0.1 C'50 units/mg.

Brief Summary Text (28):
It is a further object of the present invention to provide a gamma globulin preparation containing at least 99.0% pure immune gamma globulin which is essentially free of IgA and IgM.

Brief Summary Text (29):
It is also an object of the present invention to provide a gamma globulin preparation containing all subclasses of IgG, namely IgG.sub.1, IgG.sub.2, IgG.sub.3, and IgG.sub.4, in substantially the ratio as occurring in normal blood plasma.

Brief Summary Text (30):
A further object of the present invention is to provide an intravenous, hyperimmune globulin preparation with increased antibody titers to sixteen serospecific strains of Pseudomonas aeruginosa.

Brief Summary Text (31):
A still further object of the present invention is to provide an intravenous, hyperimmune globulin preparation with increased antibody titers to sixteen serospecific strains of Pseudomonas aeruginosa in which anticompliment activity is less than about 0.1 C'50 units/mg.

Brief Summary Text (32):
Another object of the present invention is to provide an intravenous, hyperimmune globulin preparation which is essentially free of IgA and IgM.

Brief Summary Text (33):
It is still another object of the present invention to provide a simple economical process for commercial preparation of immune gamma globulin.

Brief Summary Text (36):
According to the present invention, an unaltered, unmodified, undenatured or native immune gamma globulin preparation is provided for intravenous administration. Said preparation comprises at least 99.0% human native gamma globulin which has undergone no chemical or enzymatic modification, contains less than 0.1% IgA, essentially no IgM or aggregates and has an anticomplement activity of 0.1 or less C'50 units/mg. The immune gamma globulin preparation of the present invention consists of all the subtypes of IgG in approximately the same ratio as present in the starting material namely, about 64% IgG.sub.1, 29% IgG.sub.2, 6% IgG.sub.3 and 1% IgG.sub.4.

Brief Summary Text (37):
The anti-Pseudomonas hyperimmune globulin embodiment of the present invention, in addition to having the above-described characteristics of immune gamma globulin,

also possesses increased anti-body titers against sixteen serospecific strains of Pseudomonas aeruginosa. Hyperimmune globulin products herein referred to denote products having a greater quantity of antibodies than the quantity found in blood products obtained from un-immunized donors.

Brief Summary Text (38):
The process for the preparation of IgG includes the steps of:

Brief Summary Text (39):
a., precipitation impurities from Cohn Fraction II or plasma fraction harvested by plasmaphoresis in an aqueous-alcohol medium at a temperature of about 1.degree.-10.degree. C. and at a pH of about 7 to 9;

Brief Summary Text (43):
The concentrated solution is formulated by the addition of a salt and/or with carbohydrates. The formulated IgG is sterile filtered and dispensed in vials.

Brief Summary Text (45):
According to the present invention, the process for preparing the immune gamma globulin comprises the steps of:

Brief Summary Text (46):
a., suspending proteins present in Cohn Fraction II obtained from normal or hyperimmune plasma in an aqueous solution of about 0 to 16% w/v and preferably about about 2 to 10% w/v alcohol at a protein concentration of about 1 to 8% w/v and preferably about 1 to 4% w/v at a temperature of 1.degree.-19.degree. C. and preferably 2.degree.-5.degree. C.;

Brief Summary Text (49):
d., allowing the suspension to stand for 2 to 24 hours and preferably 6 to 18 hours to precipitate IgM, IgA, enzymes and polymeric forms of IgG impurities and to obtain equilbrium between precipitated impurities and dissolved IgG;

Brief Summary Text (50):
e., removing the precipitated impurities by filtration or centrifugation to obtain a dilute IgG solution;

Brief Summary Text (51):
f., stabilizing the dilute IgG solution by adding purified Human Serum Albumin to obtain an IgG/albumin ratio of 1/1 to 5/1 and preferably of 1/1 to 2/1;

Brief Summary Text (54):
i., concentrating the solution by ultrafiltration to obtain a concentration of 3.8 to 4.5% w.v IgG and preferably to about 4% w/v IgG;

Brief Summary Text (55):
j., removing the alcohol and concentrating the solution to about 4 to 6% w/v IgG by diafiltration; and

Brief Summary Text (57):
According to the present invention, it has been found that impurities from native IgG can be separated without the use of chemicals that tend to denature IgG under precisely established conditions which are not suggested by the prior art and not predictable from the known behavior of the compounds used in the process. The conditions essentially consist of using low ionic strength alcohol solution, and cryoprecipitation at specific temperatures and pH.

Brief Summary Text (58):
Starting Materials for the Preparation of Anti-Pseudomonas Hyperimmune Globulin

Brief Summary Text (59):
The polyvalant anti-Pseudomonas hyperimmune globulin of the present invention is produced by first isolating and combining immunizing antigens obtained from particular strains of Pseudomonas aeruginosa for use in a polyvalent vaccine which is capable of immunizing against any of sixteen recognized serotypes of Pseudomonas aeruginosa infection. Human volunteers then are vaccinated with the polyvalent vaccine to elicit responses in the antibody titers to all sixteen serotypes, followed by obtaining plasma from vaccinated donors and purification of the resultant high titer gamma globulin.

Brief Summary Text (66):
The Elisa assay employing goat anti-human immunoglobulin G(IgG) conjugated with alkaline phosphatase (Sigma Chemical Co.) and p-nitrophenyl phosphate (Sigma Chemical Co.) as a indicator system is used for measurement of antibody response to the 16 individual pseudomonas serotypes contained in The Wellcome Pseudomonas Vaccine.

Brief Summary Text (69):
A predetermined optimal dilution of anti-human IgG conjugated with alkaline phosphatase in PBS-Tween is made and 50 .mu.l is dispensed into each wall of the microtiter plates. The plates are then incubated at room temperature for one hour. After incubation, the plates are washed four times in PBS-Tween and 50 .mu.l of 1 mg/ml p-nitrophenyl phosphate in 10% diethanolamine (pH 9.8) is added. The plates are then incubated at 4.degree. C. for 18 hours.

Brief Summary Text (76):
Accordingly, the time of collection of blood from immunized donors is of an important factor in obtaining immune globulin products having a high antibody level. level. Generally, about 3 weeks post immunization the anti-body level appears to be the highest and decreases gradually thereafter.

Brief Summary Text (78):
The antibodies generated by human volunteers as a result of vaccination are harvested by plasmapheresis. Table III shows titer values on plasma pools obtained from 28 immunized donors, one group of which had high response and the other low response to immunization. It is also noted that plasma isolated from non-immunized donors also contains low titers of antibody to each of the sixteen serotypes of Ps. aeruginosa.

Brief Summary Text (79):
Purification of Polyvalent Gamma Globulin

Brief Summary Text (80):
While both plasma pools, one having low and the other high antibody titer levels, may be used to produce immune gamma globulin, high titer plasma is preferred for use use as starting material for the preparation of hyperimmune gamma globulin.

Brief Summary Text (81):
Before purification by the process of the present invention, coagulation factors, Factor VIII and Factor IX Complex are removed and the plasma subjected to Cohn fractionation. The purification procedure starts with the plasma fraction which is substantially equivalent to the Cohn Fraction II material.

Brief Summary Text (82):
Starting Materials for the Preparation of Immune Globulin (Normal Immune Globulin)

Brief Summary Text (83):
The starting material for normal immune gamma globulin may be the well-known Cohn Fraction II paste, or other starting materials having native IgG and its subclasses present. However, it is preferred to use Cohn Fraction II which has a history of

safety and efficacy as a therapeutic product in the intramuscular dosage form and is is commercially available. Alternatively, the active ingredient may be obtained by processing human plasma from which the coagulation factors, Factor VIII, and Factor IX Complex, are removed before the plasma is subjected to Cohn Fractionation. Following the removal of Factor VIII and Factor IX, the Cohn cold-ethanol fractionation produces a series of protein fractions: Fraction I, Fraction II+III, Fraction IV.sub.1 +IV.sub.4 and Fraction V. In addition to IgG, IgM and IgA, Fraction II+III is enriched in lipids, lipoproteins, pigmented materials such as carotinoids, as well as proteolytic enzymes. All of these substances must be separated from the IgG. After the separation of these undesirable substances, Fraction II is about 95% pure IgG and it represents about 40 to 50% of the IgG content of the starting plasma. Fraction II is comprised of all four subclasses of IgG, namely, IgG.sub.1, IgG.sub.2, IgG.sub.3 and IgG.sub.4, in a similar ratio as that found in plasma. The 95% pure IgG is not suitable for direct formulation into an intravenous product for several reasons. IgG is easily denatured and as such, can can form large high molecular weight aggregates. These aggregates can fix complement in the absence of antigen triggering a complement cascade which can be a risk to patients receiving intravenous infusions of IgG. The impurities amounting to to about 5% in Cohn Fraction II are also undesirable, such as: IgM, which is easily denatured and readily fixes complement; IgA, which is known to cause anaphylactoid reactions in IgA-deficient patients; Pre-Kallikrein Activator which causes vasoactive effects on administration; Plasminogen/Plasmin, which can fragment IgG and lead to reduced circulatory half-life. Cohn Fraction II, therefore, is further purified and the native character of the molecule is preserved by careful handling and stabilization as further described in detail in the method of the present invention.

Brief Summary Text (84):
Process of Preparing IgG

Brief Summary Text (85):
Cohn Fraction II paste or its equivalent is suspended and soluble portions thereof is dissolved in an aqueous alcohol solution. While the preferred alcohol is ethanol, other pharmaceutically acceptable alcohols may also be used. Subsequent to precipitating the impurities consisting of IgM, IgA, enzymes, polymeric forms of IgG and other trace contaminants, the same are removed by either filtration or centrifugation. The filtration may be accomplished by adding a diatomaceus earth filter aid, such as Hyflo-Super Cel, to the suspension, mixing the same with the suspension and filtering through 0.2 to 0.5 micron filter pads, such as Cuno 60SP. Alternatively, the precipitate may be removed by centrifugation using conventional equipment. The filtrate is concentrated by ultrafiltration over semipermeable membranes such as Pellicon system containing PT series membranes with a 10,000 or 20,000 m. w. limit in conjunction with a 1.5 micron filter, such as a Pall filter cartridge. The pH is adjusted to 7.3.+-.0.5, albumin is added to stabilize the purified gamma gloubulin and NaCl is added to improve the solubility. The alcohol is is removed from the IgG solution by diafiltration at constant volume using 5 to 10 volumes of 0.2% w/v NaCl. After the removal of the alcohol the solution is concentrated further to about 6.0% w/v IgG. The alcohol-free IgG/albumin solution is is adjusted to pH 6.9.+-.0.4 using citric acid. This solution then is diluted to contain about 5% w/v IgG by formulating the same with a salt or sugar solution. If formulated with salt, the final concentration of salt should be about 0.9% w/v. If formulated with sugar, the sugar concentration, in general, should be in the range of about 2.5 to 10% w/v. Such concentrations will vary according to the particular sugar used, for example, for monosaccharides the final concentration should be about 5.0% w/v, for disaccharides about 10.0% w/v. In addition, formulations may be made with sugar/salt combinations, such as 2.5% w/v glucose with 0.45% w/v NaCl, or 5.0% w/v sucrose with 0.45% w/v NaCl. The thus formulated IgG solution is filtered through 0.2-0.5 micron pads or cartridges, such as Cuno 60SP or Cuno IDEP, followed by filtration through a series of clarification and sterilization filters having a porosity of from 1.5 to 0.2 microns.

Brief Summary Text (86):
It is to be noted that the process of the present invention may be used to prepare a variety of hyperimmune globulin products containing hyperimmune globulin against one or more serotypes of Pseudomonas aeruginosa. In addition, the purfication process may also be used for obtaining highly purified hyperimmune gloublin that is effective against other pathogens. Still further, it is also contemplated that polyvalent immune globulin products for intravenous use having increased titers against at least two, but preferably against all sixteen, serotypes of Pseudomonas aeruginosa produced by the method of the present invention or by other appropriate art recognized methods are within the purvue of the present invention.

Detailed Description Text (3):
1 Kg Cohn Fraction II paste was suspended in 10 liters of cold purified water. The pH was adjusted to 7.5 and the suspension was allowed to stand for 4 hrs. at 2.+-.1.0.degree. C. The precipitate which contains aggregated IgG, IgM, PKa, plasminogen and other trace contaminants was removed by centrifugation at 3000.times.g for 20 min. or by filtration through a 0.2-0.5 micron filter pads such as Cuno 60 SP. The solution was adjusted to pH 6.8, stabilized by adding albumin at a ratio of 2 parts IgG to 1 part albumin, concentrated, diafiltered using 0.2% w/v NaCl and formulated by adding the desired sugar and/or salt. The solution was readjusted to pH 6.8 and diluted to a solution that had a final concentration of 5.0% w/v IgG with the desired concentration of salt and/or sugar.

Detailed Description Text (5):
1 Kg Cohn Fraction II was suspended in 15 liters of a cold purified water ethanol solution so that the final alcohol concentration was 4% w/v. The pH was adjusted to 7.6 and the suspension was allowed to stand for 2 hrs. at 2.+-.1.0.degree. C. The precipitate was removed, albumin was added at a ratio of 2 parts IgG to 1 part albumin, concentrated, diafiltered at constant volume using 0.2% w/v NaCl, and formulated by adding the desired sugar and/or salt. The pH was adjusted to 6.8 and the solution is diluted to a 5% w/v solution which contained the desired concentration of salt and/or sugar.

Detailed Description Text (7):
1 Kg Cohn Fraction II was suspended at 15 liters of cold water and alcohol was added added to the suspension to obtain a final concentration of 4% w/v alcohol. The suspension was adjusted to pH 7.6 and allowed to stand for 2 hrs. at 2.+-.1.0.degree. C. The precipitate as removed and the filtrate was adjusted to pH 6.8. Albumin is added at a ratio of 1 to 2. The solution was concentrated, diafiltered at constant volume using cold Pyrogen Free water. The solution was diluted to a 5% w/v IgG solution which contained the desired concentration of salt and/or sugar. The The pH of the solution was readjusted to pH 6.8, passed through clarification and sterilization filters, aseptically filled into sterile bottles, stoppered and sealed.

Detailed Description Text (9):
1 Kg Cohn Fraction II was suspended in 20 liters of a cold purified water-ethanol solution so that the final alcohol concentration was 4% w/v. The pH was adjusted to pH 7.4 and the suspension is allowed to stand 16 hrs. at 2.+-.1.0.degree. C. The precipitate was removed and the filtrate was adjusted to pH 6.8. Albumin was added at a ratio of 1--1 and the solution was concentrated and diafiltered at constant volume using 10 volumes of cold Pyrogen Free water at 2.+-.1.0.degree. C. The solution was then formulated by adding the desired sugar and/or salt. The pH was readjusted to 6.8 and the solution was diluted to contained a 5% w/v IgG solution that contains the desired concentration of salt and/or sugar.

Detailed Description Text (11):
Native IgG was isolated from a pool of plasma obtained from 15 non-immunized donors by Cohn fractionation and purification according to the process of the present

invention. Antibody titers of the pooled plasma and the purified gamma globulin were were measured. Side-by-side results of titers for plasma and IgG are shown for all 16 serotypes of Ps. aeruginosa in Table IV.

Detailed Description Text (13):
Native IgG was isolated from a large commercial pool (about 2,000 donors) of normal, normal, non-immunized donors and processed as in Example 5. Antibody titers of the purified gamma globulin were measured. Results are shown for all 16 serotypes of Ps. Ps. aeruginosa Table V.

Detailed Description Text (15):
Thirteen low-response donors that were immunized with polyvalent pseudomonas vaccine were selected for plasmapheresis at three weeks post vaccination. Native IgG was isolated from the plasma pool obtained from these donors as in Example 5. Antibody titers of the pooled plasma and the purified gamma globulin were measured. Side-by-side results of titers for plasma and IgG are shown for all 16 serotypes in Table VI.

Detailed Description Text (17):
Thirteen high-response donors that were immunized with polyvalent pseudomonas vaccine were selected for plasmapheresis at three weeks post-vaccination. Native IgG was isolated from the plasma pool obtained from the donors as described in Example 5. Antibody titers of the pooled plasma and the purified gamma globulin were measured. Side-by-side results of titers for plasma and IgG are shown for all 16 serotypes in Table VII.

Detailed Description Text (19):
Fifteen high-response donors that were immunized with polyvalent pseudomonas vaccine were selected for plasmapheresis at three weeks post-vaccination. Native IgG was isolated from the plasma pool obtained from the donors as described in Example 5. Antibody titers of the pooled plasma and the purified gamma globulin were measured. Side-by-side results of titers for plasma and IgG are shown for all 16 serotypes in Table VIII.

Detailed Description Text (21):
Fifteen high-response donors that were immunized with polyvalent pseudomonas vaccine were selected for plasmapheresis at eighteen weeks post-vaccination. Native IgG was isolated from the plasma pool obtained from these donors as described in Example 5. Antibody titers of the pooled plasma and the purified gamma globulin were measured. Side-by-side results of titers for plasma and IgG are shown for all 16 serotypes in Table IX.

Detailed Description Text (23):
IgG obtained in Examples 5, 6, 7, 9 and 10 were studied to determine their efficacy in the burned mouse model based on Stieritz & Holder (J. Infect. Dis. 131: 688-691, 1975). As apparent from Tables X and XI, antibody titers tend to correlate with survival of the mice infected with 10.sup.6 Ps. aeruginosa.

Detailed Description Text (24):
The products obtained by the foregoing examples, and products made according to the teaching of the specification, in addition to having been tested for antibody titers and efficacy as previously described, were tested by using appropriate procedures for verifying and defining other characteristics of IgG products. In general, the following qualities characterized the products of the present invention when analyzed according to the methods identified below.

Detailed Description Text (25):
A product of the present invention is at least 99% pure immune gamma globulin; it is essentially free of IgA and IgM as measured by Radial Immune Diffusion (RID) according to Mancini, G., Caronara, A. D., Hermans Immuno-chemistry 2 235 (1975)

and by the laser nephelometry method based on antibody-antigen complex measurements as described by Schultz et al., J. Immunological Methods 31 31-40 (1979). No plasmin plasmin or plasminogen were detected by the use of streptokinase and CBZ-lyz-P-nitrophenol, as described by the method by Silverstein, R. M. Analytical Biochemistry 65 500-506 (1975).

Detailed Description Text (26):
Anticomplement activity (ACA) is less than 0.10 C'50 units mg IgG as measured by a modified method of Kabet, E. A. and Mayer, M. Experimental Immunochemistry, Second Edition, Thomas Springfield (1961). Aggregated IgG was not detected when the product was assayed either by high performance liquid chromatograph (HPLC) using a TSK 3000 SW column or by gel permeation chromatograph using a 90 cm. column packed with LKB ultragel AcA 34. The product does not contain detectable hepatitis surface antigen B when measured by the radioimmune assay using RIASURE II test kit obtained from Electro-Nucleonics Laboratories, Inc. The product contains all the subtypes of IgG, namely IgG.sub.1, IgG.sub.2, IgG.sub.3, and IgG.sub.4, and the percentage for each of these subtypes is about 64%, 29%, 6%, and 1% respectively, which is essentially identical to the percent distribution found in the Cohn Fraction II paste as measured by Radial Immune Diffusion (RID) method referred to above. The antibody titers for measles, polio, diphtheria and hepatitis were equivalent to the titers found in the commercial intramuscular immune serum globulin products.

Detailed Description Text (27):
As earlier indicated, the pure IgG molecule obtained according to the method of the present invention is formulated into pharmaceutical dosage forms suitable for intravenous administration. Such dosage forms include the lyophilized form and the liquid dosage form of IgG.

Detailed Description Text (28):
In the lyophilized dosage form a pharmaceutically acceptable sugar such as maltose, sucrose or glucose is added to the pure product to protect the IgG and to provide bulk during freezing and lyophilization. An example for such lyophilized composition is given in Example 12, which was found to be stable for at least one year at both refrigeration and room temperatures with no change in anticomplement activity which averaged between 0.03 to 0.04 C'50 units/mg. No aggregates or fragments were detected.

Detailed Description Text (30):
Examples 13, 14 and 15 show liquid dosage formulations containing 5% w/v IgG and 2.5% w/v Normal Serum Albumin with either 10% maltose, 5% sucrose, or no carbohydrate. Appropriate amounts of sodium chloride was added in each case to make the preparations iso-osmotic.

Detailed Description Text (31):
Upon testing the maltose-containing IgG was found to be stable at room temperature for 6 months and at refrigeration temperatures for at least a year. The anticomplement activity did not change significantly from the initial levels and averaged between 0.025 and 0.045 C'50 units/mg. In addition, no aggregates or fragments were detected. The liquid formulations of IgG containing sucrose or no carbohydrates were found to be stable for at least 6 months at both refrigeration and room temperatures. The anticomplement activity did not change significantly from the initial levels, and averaged between 0.07 and 0.1 C'50 units/mg. As with the previous fromulation, no aggregate or fragments were detected.

Detailed Description Text (36):
Table XIII shows an analysis of IgG of the present invention versus that of commercial products.

Detailed Description Text (37):
The formulations of the present invention are administered intravenously.

Generally, an amount of 1 to 10 gm of gamma globulin may be used at a time. However, However, the dose of gamma-globulin for use in intravenous administration depends on on the age, physical condition, antibody titer of the particular formulation, etc. and as such the physician will determine the particular dose suitable for effecting treatment based on his considering the various factors and circumstances.

Detailed Description Paragraph Table (1):
TABLE IV Antibody Titers of Plasma and Pure IgG of Non-Immunized Donors Plasma Pool Titer Serotype (approx. 1% IgG) Titer/1% Purified IgG 1 100 200 2 400 200 3 400 200 4 100 100 5 400 400 6 25 200 7 100 100 8 100 100 9 200 100 10 200 200 11 200 200 12 50 100 13 25 100 14 400 400 15 100 200 16 200 200

Detailed Description Paragraph Table (2):
TABLE V Serotype Titer/1% Purified IgG 1 400 2 400 3 400 4 200 5 800 6 200 7 200 8 200 9 200 10 100 11 400 12 200 13 200 14 400 15 200 16 400

Detailed Description Paragraph Table (3):
TABLE VI Low-response Donors (3 weeks post-vaccination) Serotype Plasma Pool Titer Titer/1% Purified IgG 1 800 400 2 800 800 3 400 800 4 400 400 5 800 400 6 200 400 7 400 400 8 400 400 9 400 400 10 400 400 11 800 800 12 400 800 13 400 200 14 400 800 15 400 400 16 400 800

Detailed Description Paragraph Table (4):
TABLE VII High-response Donors (3 weeks post-vaccination) Serotype Plasma Pool Titer Titer/1% Purified IgG 1 800 800 2 800 1600 3 800 800 4 800 800 5 1600 1600 6 800 800 7 800 800 8 800 1600 9 800 800 10 1600 1600 11 800 1600 12 1600 3200 13 800 800 14 1600 3200 15 800 1600 16 1600 1600

Detailed Description Paragraph Table (5):
TABLE VIII High-response Donors (3 weeks post-vaccination) Serotype Plasma Pool Titer Titer/1% Purified IgG 1 800 800 2 800 800 3 800 800 4 800 800 5 800 800 6 400 800 7 400 800 8 800 800 9 800 800 10 800 1600 11 800 800 12 800 1600 13 800 800 14 1600 1600 15 800 1600 16 800 1600

Detailed Description Paragraph Table (6):
TABLE IX High-response Donors (18 weeks post-vaccination) Serotype Plasma Pool Titer Titer/1% Purified IgG 1 400 400 2 800 400 3 800 400 4 400 400 5 400 800 6 200 200 7 400 400 8 400 400 9 400 400 10 400 400 11 400 400 12 400 800 13 400 200 14 400 800 15 400 400 16 400 800

Detailed Description Paragraph Table (7):
TABLE X
Survival of Burned, Infected Mice Treated With Various Intravenous IgG Preparations (5 mg) % Survival Serotype 2/5 Treatment Examples Infective Dose 5 Days Titer None 10.sup.6 Ps. aeruginosa 0 50 Serotype 2/5 Albumin 10.sup.6 Ps. aeruginosa 0 50 Serotype 2/5 Normal Gamma Globulin 5 10.sup.6 Ps. aeruginosa 20 1350 15 Donors Serotype 2/5 Normal I.V. Gamma 6 10.sup.6 Ps. aeruginosa 60 2300 Globulin Serotype 2/5 3 Weeks Post Vaccination 7 10.sup.6 Ps. aeruginosa 60 2300 13 Refractory Donors Serotype 2/5 3 Weeks Post Vaccination 9 10.sup.6 Ps. aeruginosa 80 5600 15

Responsive Donors Serotype 2/5 18 Weeks Post Vaccination 10 10.sup.6 Ps. aeruginosa 60 2300 15 Responsive Donors Serotype 2/5

Detailed Description Paragraph Table (8):
TABLE XI
Survival of Burned, Infected Mice Treated With Various Intravenous IgG Preparations (5 mg) % Survival Serotype 6 Treatment Examples Infective Dose 5 Days Titer None 10.sup.6 Ps. aeruginosa 0 50 Serotype 6 Albumin 10.sup.6 Ps. aeruginosa 0 50 Serotype 6 Normal Gamma Globulin 5 10.sup.6 Ps. aeruginosa 0 700 15 Donors Serotype 6 Normal I.V. Gamma 6 10.sup.6 Ps. aeruginosa 0 700 Globulin Serotype 6 3 Weeks Post Post Vaccination 7 10.sup.6 Ps. aeruginosa 40 900 13 Refractory Donors Serotype 6 3 Weeks Post Vaccination 9 10.sup.6 Ps. aeruginosa 40 1800 15 RESPONSIVE DONORS Serotype 6 18 Weeks Post Vaccination 10 10.sup.6 Ps. aeruginosa 60 3600 15 Responsive Donors Serotype 6

Detailed Description Paragraph Table (9):
Ingredients gms/50 ml
Immune Globulin 2.5 Normal Serum Albumin 1.25 Sodium Chloride 0.1 Maltose 5.0 Water for Injection* q.s. to 50 ml
(*water is removed by freezedrying)

Detailed Description Paragraph Table (10):
Ingredients gms/50 ml
Immune Globulin 2.5 Normal Serum Albumin 1.25 Sodium Chloride 0.1 Maltose 5.0 Water for Injection q.s. to 50 ml

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Detailed Description Paragraph Table (11):
Ingredients gms/50 ml
Immune Globulin 2.5 Normal Serum Albumin 1.25 Sodium Chloride 0.25 Sucrose 2.5 Water for Injection q.s. to 50 ml

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Detailed Description Paragraph Table (12):
Ingredients gms/50 ml
Immune Globulin 2.5 Normal Serum Albumin 1.25 Sodium Chloride 0.45 Water for Injection q.s. to 50 ml

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Detailed Description Paragraph Table (13):
TABLE XII
Analysis of IV-IGG Lots Immuneglobulin Composition ACA Mol. Size Lot No. Description % IgG % IgA % IgM C'50 U/mg % Aggregate 1 Lyophylized 100 0 0 0.040 0 10% Maltose 2 10% Maltose 99.87 0.03 0 0.049 0 3 5% Glucose 99.97 0.03 0 0.053 0 4 10% Maltose 100 0 0 0.045 0 5 10% Maltose 99.97 0.03 0 0.030 0 6 Saline 99.97 0.03 0 0.082 0 7 5% Sucrose 99.96 0.04 0 0.077 0 8 Saline 100 0 0 0.088 0 9 10% Maltose 99.95 0 0 0.033 0 10 10% Maltose 99.91 0.09 0 0.041 0 11 5% Maltose 99.96 0.04 0 0.087 0

Detailed Description Paragraph Table (14):
TABLE XIII
ANALYSIS OF IgG of the PRESENT INVENTION VS COMMERCIAL IgG PRODUCTS IgG IgA IgM IgG.sub.2 IgG.sub.3 IgG.sub.4 ACA Pka Manufacturer Mg/dl mg/dl mg/dl IgG.sub.1 % % % C'50/mg

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Tackling anthrax.

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